

REMARKS

Upon entry of the above amendments, claims 20-39 will be pending, claims 1-19 having been canceled without prejudice and new claims 20-39 added. Support for the new claims can be found throughout the specification. For example, support for claim 20 can be found at page 2, lines 24 to 28; page 4, lines 11 to 12; page 6, lines 30 to 33; page 7, lines 17 to 24; page 27, lines 1 to 17; and Figures 2 to 8. Support for claim 21 can be found at, for example, page 1, line 37 to page 2, lines 2 and 13 to 18; page 4, lines 2 to 3 and 11 to 12; page 27, lines 1 to 17 and 20 to 22; and Figures 2 to 8. Support for claim 22 can be found at, for example, page 2, lines 29 to 30; page 4, lines 23 to 31; and Figure 2. Support for claims 23, 25 and 36 can be found at, for example, page 11, line 31 to page 12, line 5 and page 12, lines 7 and 9 to 36. Support for claims 24, 26 and 37 can be found at, for example, page 2, lines 7 and 14 to 15; page 11, line 31 to page 12, line 5; page 26, line 30 to 31; and Figures 2 to 8. Support for claims 27 and 28 can be found at, for example, page 12, lines 9 to 36. Support for claims 29 to 33 and claims 38 and 39 can be found at, for example, page 5, lines 7 to 11; page 5, line 19 to page 6, lines 21 to 29; and page 8, lines 15 to 16. Support for claim 34 can be found at, for example, page 4, lines 29 to 34; page 5, lines 1 to 2; page 8, lines 10 to 11; and Figure 2. Support for claim 35 can be found at, for example, page 4, lines 17 to 21. The new claims would add no new matter to the application.

Interview Summary

As a first matter, Applicants wish to thank Examiner Gussow and her supervisor for speaking with the undersigned and her colleague Adam Kerstien by telephone on June 25, 2008, regarding a set of proposed new claims 20-39 that are largely as presented above. During that interview, written description support for the proposed new claims was discussed, and the Examiner and her supervisor agreed that there was sufficient support for the claims as presented above. In response to a question from the Examiner regarding the nature of the diabody defined in claim 20 (i.e., the diabody used as the comparator), applicants pointed out that the heavy chain variable fragment sequences and light chain variable fragment sequences comprising both the scFv multimer and the comparator diabody are derived from the same antibody.

The Examiner agreed that the subject matter of the proposed new claims 20-39 is within the elected restriction group that is presently under examination. However, she indicated that the lists of antigens in proposed new claim 28 may require a new restriction requirement, with one antigen per restriction group. After some discussion, it was agreed that if any linking claim is deemed allowable, then the entire scope of claim 28 would also be deemed allowable (essentially treating the restriction as a species election). If the Examiner does decide to impose the new restriction requirement as discussed, applicants hereby elect the claim 28 species myeloproliferative leukemia virus oncogene (mpl) as the species for initial examination. Mpl is a member of the hematopoietic receptor family, one of the families listed in new claim 27. All of the new claims 20-39 read on this elected species.

Finally, the fundamental structural differences between a diabody and a sc(Fv)2 were discussed, as understanding those structural differences is important for understanding how the present invention is distinguished over the prior art cited in the outstanding Office action. As applicants pointed out, while both a diabody and a sc(Fv)2 possess two light chain variable regions and two heavy chain variable regions, in a diabody the four variable regions are in two non-covalently associated scFv molecules, while a sc(Fv)2 molecule contains all four variable regions in a single, linear polypeptide chain. This distinction between a diabody and a sc(Fv)2 is consistent with how those terms are used in the specification (see, e.g., page 4, lines 17-28, and also at page 26, lines 13-14, where it is disclosed that in a gel run under reducing conditions, the diabody (which would be dissociated into two single chains under reducing conditions) ran at about half the size of the sc(Fv)2. It is also consistent with the definition of "diabody" in Atwell et al., Protein Engineering, 12:597-604 (1999), quoted in footnote 1 below.

The substance of the rejections in the Office action were not addressed in the telephone conference, applicants electing instead to address those rejections in these written comments.

Priority

The Office action at pages 2-3 states, "Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d), a certified English translation of the foreign application must be submitted in reply to this action." Applicants enclose such a certified

English translation of the Japanese priority document, Japanese Patent Application No. 2003-415760. However, it is noted for the record that the present application is a national phase of International Application No. PCT/JP2004/018493. It was filed under 35 U.S.C. § 371, and not under 35 U.S.C. § 119. Thus, it is entitled to the benefit of foreign priority regardless of whether an English translation of the priority document is on file.

Rejections under 35 U.S.C. §102

The Office action rejects claims 1-3, 5 and 6 under 35 U.S.C. §102(b) as allegedly anticipated by Tahtis *et al.* According to the Office action at page 4, “Tahtis, et al. teach a method for producing a diabody comprising two identical scFv molecules – sc(Fv)₂ – in which the V_H and V_L domains are linked by a five amino acid residue linker. Tahtis, et al. teach the diabody had increased uptake relative to the F(ab')₂ fragment.” Claims 1-3, 5 and 6 have been cancelled, so the rejection is moot as to them. To the extent that a similar rejection may be applied to the present claims, applicants traverse.

The Examiner correctly notes that Tahtis *et al.* teach a method for producing a diabody comprising two scFv molecules in which the V_H and V_L domains are linked by a five amino acid residue linker (Tahtis *et al.*, p. 1062, col. 1, last paragraph to col. 2, first paragraph). As explained above, a diabody contains two non-covalently associated scFv polypeptides.¹ (The five amino acid residue linker taught by Tahtis *et al.* is, of course, between the V_H and V_L domains *in the scFv*, and not *between* the two scFv. The two identical copies of the scFv that comprise the diabody in Tahtis *et al.* are *non-covalently* associated.) Because applicants do not claim a method for producing a diabody, this teaching of Tahtis *et al.* does not anticipate any claim. Each of the independent claims 20, 21, 35 and 39 is individually addressed below.

New independent claim 20 is drawn to a method comprising a step of producing a covalently linked scFv multimer comprising two or more copies of the light chain variable region

¹ Tahtis *et al.* synthesized their diabodies as described in reference 21 (Tahtis *et al.*, p. 1062, col. 1, last paragraph; citing to Atwell *et al.* Protein Engineering, 1999, Vol. 12, pages 597-604). Atwell *et al.* (attached as Exhibit A) states in relevant part, “a single-chain molecule (scFv) [is a molecule] in which the V_H and V_L domains of the antibody are joined by a flexible polypeptide....As the linker is shortened to <12 residues, the V_H domain is unable to bind to its attached V_L domain in the Fv orientation. Instead, complementary V_H/V_L pairs *from two separate scFv molecules* combine to form a bivalent dimer, termed a diabody.” (Atwell, *et al.*, p. 597, col. 1, emphasis added).

sequence and two or more copies of the heavy chain variable region sequence. Though a “diabody” is mentioned in claim 20, it is mentioned only as a comparator to aid in defining the activity level of the covalently linked scFv multimer. As Tahtis *et al.* does not disclose a covalently linked multimer (sc(Fv)₂ or otherwise) as required by claim 20, Tahtis *et al.* does not anticipate claim 20 nor any claim that depends therefrom.

New independent claim 21 is drawn to a method comprising a step of producing a single-chain polypeptide comprising two or more copies of a light chain variable region sequence and two or more copies of a heavy chain variable region sequence. Though a “diabody” is mentioned in claim 21, it is mentioned only as a comparator to aid in defining the activity level of the single-chain polypeptide of step (c). As Tahtis *et al.* does not disclose a single chain polypeptide meeting the criteria of claim 21, Tahtis *et al.* does not anticipate claim 21 nor any claim that depends therefrom.

New independent claim 35 is drawn to a method comprising a step of producing a sc(Fv)₂ comprising the light chain variable region sequence and the heavy chain variable region sequence of a first antibody and the light chain variable region sequence and the heavy chain variable region sequence of a second antibody, all linked via linkers into a single-chain polypeptide. Though a “diabody” is mentioned in claim 35, it is mentioned only as a comparator to aid in defining the activity level of the sc(Fv)₂ of step (c). As Tahtis *et al.* does not disclose a sc(Fv)₂ (much less a divalent sc(Fv)₂ containing variable domains derived from two different antibodies), Tahtis *et al.* does not anticipate claim 35 nor any claim that depends therefrom.

New independent claim 39 is drawn to a method comprising a step of producing a single-chain polypeptide comprising two or more copies of a humanized version of a light chain variable region sequence and two or more copies of a humanized version of a heavy chain variable region sequence, linked via linkers. Though a “diabody” is mentioned in claim 39, it is mentioned only as a comparator to aid in defining the activity level of the single-chain polypeptide of step (c). As Tahtis *et al.* does not disclose a single chain polypeptide that contains two or more copies of a light chain variable region and two or more copies of a heavy chain variable region, Tahtis *et al.* does not anticipate claim 39.

The dependent claims, of course, contain additional limitations that provide further distinctions over Tahtis *et al.*: see, e.g., the requirement in claims 24, 26, and 37 that the antigen is mpl and the requirement in claims 23, 25, and 36 that the activity is an agonist activity.

For at least the reasons stated above, Applicants request that the rejection based on Tahtis *et al.* be withdrawn.

Claims 1-8 and 13 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Orita *et al.* The rejection is moot as to those claims, as they have been canceled. To the extent that the rejection may be applied to the presently pending claims, applicants traverse.

The publication date shown on the face of Orita *et al.* is January 15, 2005. The present application is a U.S. national phase application having a PCT filing date of December 10, 2004, so Orita *et al.* plainly is not citable as prior art. Furthermore, the present application claims priority to Japanese Patent Application No. 2003-415760, filed on December 12, 2003. Applicants enclose a certified English language translation of the Japanese priority application as proof that the claims are entitled to that 2003 priority date. For at least these reasons, applicants request that the rejection based on Orita *et al.* be withdrawn.

Claims 1-8 and 13 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fukushima *et al.* According to the Office action at page 5,

Fukushima, et al. teach production of sc(Fv)₂ diabodies comprising two VH and two VL domains linked by a polypeptide linker having between 5 and 15 amino acids (figure 38). Fukushima, et al. teach the scFv antibody had 400-fold stronger agonist activity compared with the monovalent sc12B5 antibody (paragraph 306).

As claims 1-8 and 13 have been canceled, the rejection is moot as to them. To the extent that the rejection may be applied to the presently pending claims, applicants traverse.

The Office action points to Fig. 38 of Fukushima *et al.* as teaching “production of sc(Fv)₂ diabodies comprising two VH and two VL domains linked by a polypeptide linker having between 5 and 15 amino acids.” In fact, Fig. 38 has nothing to do with sc(Fv)₂, but rather illustrates different linkers used to link one light chain variable region to one heavy chain variable region, thereby generating an scFv (not sc(Fv)₂). As explained by Fukushima *et al.*, e.g., in paragraph 0306, the scFv can exist as scFv monomers or pair off into non-covalently

associated dimers (i.e., diabodies), each dimer containing two copies of the scFv monomer. These scFv dimers (the term Fukushima *et al.* uses instead of "diabodies") should not be confused with sc(Fv)2, which as explained above consist of a single polypeptide chain instead of two, and so are structurally distinct from diabodies.

Applicants note that Fukushima *et al.* elsewhere does in fact disclose a comparison among a full-length antibody (MABL-2), a corresponding scFv dimer (i.e., diabody), and a corresponding sc(Fv)2 in assays for apoptosis-inducing activity. As described in paragraph 0262 and Fig. 43 of Fukushima *et al.*, the sc(Fv)2 polypeptide derived from MABL-2 was more active than the parental IgG but less active than the corresponding diabody "MABL2-scFv <HL-5>" in inducing apoptosis in either of two types of cells. Since each of the present claims requires a covalently linked scFv multimer (claim 20) or single-chain polypeptide (claims 21 and 39) or sc(Fv)2 (claim 35) that has a greater level of activity than the corresponding diabody, Fukushima *et al.* does not anticipate any of the present claims. If anything, the activity level of the MABL-2-derived sc(Fv)2 of Fukushima *et al.* is the *inverse* of what is claimed, thereby teaching away from the presently claimed methods.

For at least the reasons stated above, Applicant requests that the rejection based on Fukushima *et al.* be withdrawn and all claims allowed.

Please apply any necessary charges or any credits to deposit account 06-1050.

Respectfully submitted,

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